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Transcranial sonography in psychiatric diseases

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Abstract Transcranial sonography (TCS) revealed reduced echogenicity of the brainstem raphe (BR) as a characteristic finding in unipolar depression and in depression associated with Parkinson's or Wilson's disease, but not in healthy adults, schizophrenia, multiple sclerosis with depression or Parkinson's disease without concomitant depression. Similar findings were shown also for adjustment disorder with depressed mood. In contrast to unipolar depression, sonographic findings of bipolar patients may generally indicate preserved structural integrity of mesencephalic raphe structures. If bipolar disorder is associated with hypoechogenic BR, depressive symptoms are more severe. BR hypoechogenicity could be caused by a modification of tissue cell density, the interstitial matrix composition or an alteration of fiber tracts integrity representing involvement of the basal limbic system in the pathogenesis of unipolar depression and depression associated with certain neurodegenerative diseases.

Recently it was shown that nigrostriatal dopaminergic system is abnormal in children with attention-deficit hyperactivity disorder which was expressed by significantly larger echogenicity of substantia nigra.

The increasingly broad application of TCS in the early and differential diagnosis of neurodegenerative and psychiatric disorders in many centers all over the world is probably the best evidence for the value of the method. Main advantages include the easy applicability, the fact that it is quick and repeatedly performable with no limitations as known from other neuroimaging techniques and that it is relatively cheap and side effect free.

Transcranial sonography — historical overview and method in psychiatric diseases

Transcranial sonography (TCS) is a relatively new neuroimaging method which displays tissue echogenicity (intensity of reflected ultrasound waves) of the brain through the intact skull.

Besides the specific finding of the substantia nigra (SN) hyperechogenicity in Parkinson's disease (PD), first time described in 1995 by Becker et al. [1], a series of studies using TCS has reported another specific ultrasound feature: structural abnormality of the midbrain raphe depicted as reduced echogenicity or invisible brainstem raphe (BR) in patients with unipolar depression compared with healthy individuals [2,3]. The structural abnormality which was reported to occur in unipolar depressed patients, was unrelated to severity of current illness, and was absent in patients with schizophrenia [3]. The same structural abnormality has also been reported when depressed patients have been compared to non-depressed patients, having a variety of neurological diseases, for example, PD [4,5], dystonic

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syndromes [6] and Wilson's disease [7] but not multiple sclerosis with or without depression [8,9]. Modern clinical TCS systems display deep echogenic brain structures with a high image resolution of up to 0.7 mm × 1 mm which is even higher than that of magnetic resonance imaging (MRI) under clinical conditions [10]. Meanwhile, consensus guidelines for standardized procedure of TCS of midbrain structures, basal ganglia and ventricles have been established [11,12], allowing standardized scanning procedure and comparability of TCS findings between different research groups.

TCS of brain structures is performed through the temporal acoustic bone window, with preauricular position of the ultrasound probe parallel to the orbitomeatal line. Modern clinical ultrasound systems equipped with 2.0- to 3.5-MHz transducers can be applied [11,12]. The parameter settings of the TCS system should be chosen as follows: dynamic range 45—60 dB, insonation depth 14—16 cm, time gain compensation and image brightness are adapted as needed for the best visualization. When the brain structure of interest is clearly displayed, the image should be fixed and zoomed in two- to three-fold for further measurements [11]. The examination is performed at axial scanning planes through the midbrain and the thalami [11,12]. The mesencephalic brainstem can be depicted as a butterfly shaped structure of low echogenicity surrounded by the highly echogenic basal cisterns. The echogenicity of the ipsilateral SN, red nucleus (RN) and the BR could be evaluated (Fig. 1). The BR is usually seen as a highly echogenic continuous line with an echogenicity that is identical to that of the RN [13]. Echogenicity of BR is rated semiquantitatively, using either a 3-point (grade 1: raphe invisible; grade 2: slightly echogenic or interrupted BR; grade 3: high echogenicity identical to that of RN or basal cisterns) or, preferably, a 2-point (grade 0: invisible, hypoechogenic or interrupted BR; grade 1: highly echogenic BR as a continuous line) grading system [13]. It is important to scan the subject investigated from both sides, as the bone window may vary allowing sufficient visualization of the BR only if both sides are considered. Therefore, if the BR can be depicted as continuous line from one side, it is rated as a normal (grade 1) — that is, hyperechogenic, non-interrupted continuous line.

Changes in raphe echogenicity reflect changes in tissue impedance and point towards an alteration of the brainstem microarchitecture which could be due to a shift in tissue cell density, a change in interstitial matrix composition, or an alteration of fiber tract integrity [5,14]. Various anatomical, physiological, and biochemical findings underline the importance of the basal limbic system in the pathogenesis of affective disorders, and compelling evidence suggests that the nuclei, fiber tracts, and neurotransmitter systems associated with the basal limbic system are involved in the pathogenesis of primary depression and depression associated with some neurodegenerative diseases such as PD [15,16]. The change of acoustic impedance, which is recorded by TCS as reduced BR echogenicity, might be the result of microstructual changes, gliosis and disruption of fiber tract integrity [14].

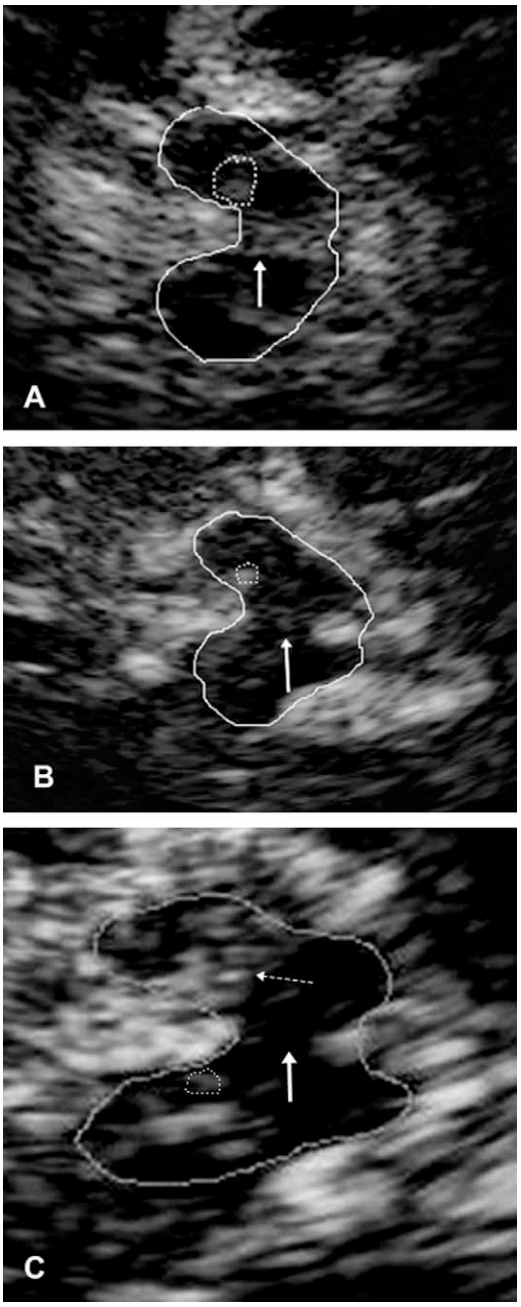

Figure 1 Sonographic images of corresponding midbrain axial sections in three subjects. The butterfly-shaped hypoechognic midbrain was encircled for better visualization (full line). Thick arrows indicate brainstem raphe; red nucleus is encircled with dotted line. (A) Mesencephalic brainstem of a healthy individual with normal, highly echogenic brainstem raphe as a continuous line which has the same echogenicity as the red nucleus. (B) Mesencephalic brainstem of a patient with unipolar depression with interrupted, reduced echogenicity of the brainstem raphe. (C) Mesencephalic brainstem of a PD patient with depression displays marked hyperechogenicity of the substantia nigra (thin dotted arrow) and invisible brainstem raphe (thick full arrow).

TCS in unipolar depression

Numerous evidence from neuroimaging, biochemical and animal studies implicates basal limbic system and raphe

nuclei involvement in the pathogenesis of the mood disorders, particularly depression. Typical ultrasound marker that can be of value in the diagnosis and differential diagnosis of depression is the low echogenicity or interrupted BR. Raphe hypoechogenicity is a common finding in 50—70% of patients with unipolar depression [2,17] and is associated with responsivity to serotonin-reuptake inhibitors (SSRI) [18]. In a pioneer study, echogenicity of the BR was examined by TCS in 20 patients with unipolar depression and 20 healthy adult controls. A marked reduction of raphe echogenicity in depressed patients was found [2]. This finding was confirmed a year later on larger number of patients in the study which compared echogenicity of the BR between 40 patients with unipolar depression, 40 patients with bipolar disorder and 40 healthy controls. Raphe echogenicity in patients with unipolar depression was found to be distinctly reduced as compared with healthy adults and patients with bipolar affective disorder. BR echogenicity, on average, was halved in the unipolar depressed group. No correlation was found between BR echogenicity and age, sex or disease severity [3]. Reduced brainstem midline echogenicity of depressed patients was interpreted as a structural alteration of the dorsal raphe nucleus or fiber tracts in this region [14]. Increased T2-relaxation time in a pontine brainstem in patients with major depression could be in line with previous reports of brainstem pathology in these patients [14]. The observation might indicate a subtle tissue alteration, which cannot be identified by visual inspection of the images. T2-relaxation time depends on physical tissue characteristics and is influenced by hydration status or iron content. Differences in T2-relaxation time of specific brain areas between patients with major depression and healthy controls may indicate different tissue composition caused by histological changes.

Several further studies confirmed the finding of reduced echogenicity of the BR in unipolar depression. In the study of Walter [17] the frequency of patients with reduced echogenicity of BR was higher in unipolar depression compared with healthy individuals and in depressed PD patients compared with non-depressed. The frequency of reduced echogenicity of BR was the highest in patients with unipolar depression. In this study, reduced echogenicity of the BR was more frequent in depressed than in non-depressed patients, irrespective of presence of PD.

TCS findings of another study [19], showed that reduced echogenicity of pontomesencephalic BR is frequent in depressive states, irrespective of diagnostic category of depression, but only rare in healthy subjects without any history of psychiatric disorder. BR echogenicity could not discriminate between major depressive disorder and adjustment disorder with depressed mood. BR echogenicity scores showed in this study were significantly lower in SSRI responders compared with SSRI non-responders. Reduced BR echogenicity indicated SSRI responsivity with a positive predictive value of 88%.

Recently, reduced raphe echogenicity was found in 47% of the patients with major depressive disorder but only in 15% of healthy controls. In patients with suicidal ideations that finding was even more pronounced (86%) with the highest frequency of completely not visible TCS raphe finding (72%). Data showed that altered echogenicity of the BR is frequent in patients with suicidal ideation. Normal raphe echogenicity in patients with major depression was associated with less severe depressive symptoms and rarely with the presence of suicidal ideations [20].

Although there are several reports of MRI signal alteration of BR in depression, a characteristic neuroimaging pattern of BR abnormality has not yet been found [21].

Ultrasound investigations have been supplemented by T2-weighted MRI studies in order to investigate pathomorphological pattern of the BR in depression. Increased intensity of the midline has been reported for unipolar depressed patients when compared to bipolar patients and controls in a retrospective study using T2-weighted MRI [22]. A difference between patients with major depression and control subjects for T2-relaxation times was found in a region of interest located along the midline of the pons. No difference was found between patients with bipolar disorder and control subjects. Alterations of T2-relaxation times might indicate subtle tissue changes [23]. These findings are in line with the results of pathoanatomic and PET studies demonstrating morphological and functional alteration of the dorsal raphe nucleus in major depression, with decreased serotonin type 1A receptor binding and fewer neurons expressing serotonin transporter mRNA compared with findings in controls [24]. The relationship of BR echogenicity and SSRI responsivity which was found in the study of Walter [19] further supports the idea that reduced BR echogenicity reflects an alteration of the serotonergic system.

In contrast with previous reports, no difference in echogenicity of the BR of unipolar depressed patients was found in the study of Steele, the only one which investigated possible structural changes of the BR in unipolar depression using diffusion tensor imaging, did not confirm structural changes of the BR in unipolar depressive patients using this method [25]. One of the important advantages of TCS is that it could also detect a subgroup of patients with depression characterized by mild clinical signs of parkinsonism who are possibly at an elevated risk of developing definite PD.

TCS data in a recent study showed that the finding of SN hyperechogenicity, which is characteristic for idiopathic PD, was related to motor asymmetry and reduced verbal fluency in patients with depressive disorders. This relationship was even stronger in younger patients (<50 years) and independent from age, in patients who had reduced BR echogenicity [21]. Since, both liability for developing PD and frequency of PD-like TCS findings were found to be increased in depression, patients with depressive disorders might be an important population to screen for sonographic and clinical signs of early PD.

TCS in adjustment disorder with depressed mood (ADDM)

Major depressive disorder (MDD) and adjustment disorder with depressed mood (ADDM) are currently regarded as distinct disease entities [26]. Especially, DSM axis-II comorbidity and suicidal behavior have been reported to differ between MDD and ADDM. Following the Structured Clinical Interview for DSM-IV Axis-I Disorders [27], in the study performed by Walter et al. [18], 15 patients with single episode of MDD (MDDs), 22 with recurrent MDD (MDDr)

and 15 with ADDM. Reduced BR echogenicity was found in 54% of the patients with MDD and ADDM, but only in four (8%) of the healthy subjects. BR echogenicity scores did not differ among patients with MDDs, MDDr, or ADDM, and pair-wise group comparisons failed to show differences between diagnostic groups with respect to frequency of reduced BR echogenicity. TCS findings of this study showed that reduced echogenicity of pontomesencephalic BR is frequent in depressive states, irrespective of diagnostic category. As a result of the present study, the hypothesis that BR echogenicity might distinguish patients with MDD and patients with ADDM had to be rejected. Reduced BR echogenicity is found with similar frequency in MDDs, MDDr, and ADDM. This is in agreement with results of clinical and neurophysiological studies suggesting common pathophysiological mechanisms in MDD and ADDM [28].

TCS in bipolar disorder

Bipolar affective disorders are characterized by recurrent episodes of depression as well as mania or hypomania [26]. In histological studies, subtle structural deficits in the dorsal raphe with a regional reduction in the synthesis of noradrenalin have been described in patients with bipolar disorder. The first TCS study evaluated BR alterations in patients with bipolar affective disorders, revealed normal or even increased echogenicity of BR in bipolar disorder, irrespective of the existing disease conditions. This observation led to the assumption that reduced echogenicity of BR may be specific to unipolar depression [3]. Recently, Krogias et al. found the BR hypoechogenicity in 36.1% of the 36 patients with bipolar I disorder (14 depressed, 8 manic, 14 euthymic) and in 20% of the 35 healthy controls. Compared to the control group, frequency of altered BR echogenicities did not reach statistical significance. Hypoechogenicity of BR was depicted in six (42.9%) of the depressed, in three (37.5%) of the manic and in four (28.6%) of the euthymic bipolar patients, with no significant difference between the three subgroups [29].

The width of third ventricle was significantly larger in the patient group (3.8 ± 2.1 mm vs. 2.7 ± 1.2 mm). Depressed bipolar patients with reduced BR echogenicity showed significantly higher scores on the Hamilton Depression Rating Scale as well as the Montgomery-Åsberg Depression Rating Scale [29].

Relating to echogenicity of SN, a strong trend of more frequent SN hyperechogenicities in the depressed subgroup was identified. Hyperechogenic SN was seen in six patients (16.7%): five (35.7%) of the depressed, in none (0%) of the manic and in one (7.1%) of the euthymic patients, indicating cyclical dysregulation in quantitative dopaminergic transmission as one of the underlying pathologies in the pathogenesis of bipolar disorder.

One of the main conclusions to be drawn from the study is that sonographic findings do not differ in different mood states of bipolar I disorder. Regarding the brainstem raphe, hypoechogenicity is correlated to the severity of symptoms in bipolar depression. Furthermore, bipolar patients in general showed significantly larger widths of the third ventricle than the control group in this study [29].

TCS in attention-deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) is frequent neuropsychiatric disorder characterized by excessive motor activity, increased impulsivity and attention deficits. Hypotheses about its pathophysiology implicate various neurotransmitters including dopamine [30]. One recent study investigated echogenicity of the SN as a potential structural marker for dysfunction of the nigrostriatal dopaminergic system in children with ADHD. Echogenicity of the SN in this study was determined in 22 children with DSM-IV diagnosis of ADHD and 22 healthy controls matched for age and sex. The echogeniciity of SN was significantly larger in ADHD patients than in healthy controls ($F_{1,42} = 9.298$, $p = 0.004$, effect size = 0.92, specificity was 0.73 and sensitivity 0.82) without effects of age or sex. The study showed that nigrostriatal dopaminergic system is abnormal in children with ADHD. Increased SN echogenicity in ADHD patients relative to healthy controls might be explained by a developmental delay. Although most findings with regard to a presumptive developmental delay in ADHD relate to diminished growth of cortical thickness, recent studies have reported structural alterations in the basal ganglia of patients with ADHD. It remains unclear whether an enlarged echogenic SN area in ADHD patients can be attributed to a primary disturbance of nigral iron metabolism, whether it is related to a primary developmental delay of brain structure, or whether it indicates a general structural marker for dysfunction of the dopaminergic system [31].

Conclusion

The increasingly broad application of TCS in the early and differential diagnosis of psychiatric and neurodegenerative diseases in many centers all over the world is probably the best evidence for the value of the method. The main advantages include the easy applicability, even in moving (e.g. tremulous or agitated) patients, the fact that it is quick and repeatedly performable with no limitations as known from other neuroimaging techniques (metal in the body as a limitation for MRI imaging, specific medication as a limitation for many forms of functional neuroimaging), and that it is relatively cheap and side effect free.

It is a reliable method to investigate, diagnose and follow-up patients with unipolar depression, bipolar disorder, ADHD and depression associated with some neurodegenerative diseases.

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